

I. Matters of definiteness

The Examiner has rejected claims 1, and 3-33 under 35 U.S.C. § 112, second paragraph on the assertion that the recitation of the term "location" in claim 1 and 14 (and their dependent claims) is not clear, citing a definition from The American Heritage Dictionary of the English Language (4th ed.) for the term. Claims 1 and 14 currently recite the phrase "formation of a metallic precipitate in one or more discrete regions", rendering the previous rejection inapplicable. Thus, Applicants respectfully request withdrawal of the rejection to the claims under 35 U.S.C. § 112, second paragraph.

II. The claimed invention is novel

The Examiner has rejected claims 1, 6, 28 and 33 under 35 U.S.C. § 102(e) on the assertion that Lockhart *et al.* (USP 6,344,316) anticipates the claims. Specifically, the Examiner asserts that Lockhart *et al.* discloses a method for detecting nucleic acids using an oligonucleotide array, labeling the targets with different means including colloidal gold (see col. 24) and that the target sample is a biological sample (see col. 2, line 34).

M.P.E.P. 2131 requires that, in order to anticipate a claim, the reference must teach every element of the claim. Amended Claim 1 includes the step of "performing a catalytic reduction of a metal present in solution leading to formation of a metallic precipitate in one or more discrete regions." There is no teaching within Lockhart *et al.* of a method which includes the catalytic reduction of a metal leading to the formation of a metallic precipitate as recited in amended Claim 1. In contrast to the metallic precipitates formed by the catalytic reduction of a metal recited in Claim 1, Lockhart *et al.* disclose a colorimetric label (e.g. colloidal gold) about 40-80 nm in size and able to scatter green light. Because Lockhart *et al.* does not disclose catalytic reduction of a metal to form a metallic precipitate, Applicants submit that Lockhart *et al.* does not anticipate Claim 1.

Furthermore, Applicants note that formation of a metallic precipitate was recited in Claim 2, which was not asserted to be anticipated by Lockhart *et al.* In view of the foregoing, Applicants respectfully request withdrawal of the rejection to claims 1, 6, 28 and 33 under 35 U.S.C. § 102(e).

III. The claimed invention is non-obvious

The Examiner rejected the claims under 35 U.S.C. § 103(a) on the assertion that the following cited references anticipate the invention as claimed.

In order for a combination of references to render a claim obvious, the combination of references must teach or suggest each of the elements of the claimed invention and must also provide the motivation to combine these elements to create the claimed invention. *In re Fine*, 5 U.S.P.Q.2d 1597 (Fed. Cir. 1988), *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1456 (Fed. Cir. 1998) and *In re Geiger*, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), *In re Dembiczak* (175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999) As discussed below, the cited combination of references does not suggest all of the elements of the claimed invention, nor does the cited combination of references provide a motivation to combine the elements to create the claimed invention. Furthermore, as discussed below, the claimed invention provides significant advantages over the methods disclosed in the cited references.

Lockhart et al. in view of Van Ness et al.

Claims 1, 7-9 and 28 are rejected under 35 U.S.C. § 103(a) over Lockhart et al. (USP 6,344,316) in view of Van Ness et al. (USP 6,027,980). Specifically, the Examiner asserts that one of skill in the art would be motivated to combine Lockhart et al. with Van Ness et al. to arrive at the presently-claimed invention with a reasonable expectation of success.

As discussed above, Lockhart et al. does not teach or suggest the catalytic reduction of a metal leading to the formation of a metallic precipitate as required by amended Claim 1 of the present invention.

Furthermore, Van Ness et al. does not teach or suggest the catalytic reduction of a metal to form a metallic precipitate. In contrast, Van Ness et al disclose methods in which a tag is cleaved from a probe and detected using non fluorescent spectrometry or potentiometry.

Because neither Lockhart et al. nor Van Ness et al teach or suggest the catalytic reduction of a metal, Applicant maintains that the cited references do not render the claimed invention obvious.

Abouzied et al. in view of Howard III et al. and Van Ness et al. and further in view of Roth et al. and Terstappen et al.

Claims 1-26 stand rejected under 35 U.S.C. § 103(a) over Abouzied et al. in view of Howard III et al. and Van Ness et al. and further in view of Roth et al. and Terstappen et al. The Examiner asserts that the Office Action of 2/22/01 outlines the teaching/suggestion to combine these cited references to arrive at the presently claimed invention, further stating that the term "location" in [prior] claim 1 renders the claim and its dependents indefinite.

As stated above, the method of amended claim 1 includes "...performing a catalytic reduction of a metal present in solution leading to formation of a metallic precipitate in one or more discrete regions..."

The Abouzied et al. reference discloses a colorimetric method of screening and detecting analytes on nitrocellulose (NC) membrane strips. In the method described in Abouzied, a colored reaction product formed through the action of an enzyme linked to the target analyte is used to detect the presence of the analyte in the sample. Abouzied does not teach or suggest methods in which a metallic precipitate is formed by the catalytic reduction of a metal. The method of detection includes visually comparing color intensities formed by precipitates on the NC membrane and quantitatively assaying line density using a CCD camera. In addition, in the method disclosed in Abouzied, the lines on the NC membrane strips were spaced 0.25 cm apart (page 496, column 2). As indicated in the specification at page 2, line 32 through page 3, line 11, colorimetric assays in which an enzyme generates a colored reaction product which forms a precipitate, such as the methods described in Abouzied, are unsuitable for use in arrays comprising a density of at least 20 discrete regions per cm^2 because the precipitate occupies an area which is too large to allow it to be localized to one or more discrete region(s). This is acknowledged in the 2/22/01 Office Action (see page 5) where the Examiner states that "...the dimension of the line blots disclosed does not allow a density of 20 or more discrete regions per cm^2 with each region having one species of capture molecule..."

With respect to the apparatus of claim 14, Applicants note that Abouzied et al. discloses a nitrocellulose strip being visualized by a camera which is connected to a computer to detect and/or quantify. However, the nitrocellulose strip of Abouzied, as previously discussed, is not a solid support comprising an array of at least 20 discrete regions per cm^2 . Furthermore, there is no teaching or suggestion Abouzied of a catalytic reduction of a metal to form a metallic precipitate.

Howard III et al. disclose a video test strip reader for detecting the presence of molecules bound to a test strip. The device of Howard is not used to detect a metallic precipitate formed on a high density array as in the present invention but rather to read a signal from a test strip. There is no disclosure or suggestion of detecting the presence of a metallic precipitate formed at one or more discrete region(s) on an array having a density of at least 20 discrete regions per cm^2 as in the present invention or devices comprising such arrays and such precipitates.

Furthermore, with respect to the apparatus of claim 14, while Howard III et al. discloses a CCD camera equipped with illumination sources and a computer system (see page 5) which can evaluate such information as barcodes. The apparatus disclosed in Howard is used with a test strip rather than an array having a density of at least 20 discrete regions per cm^2 and does not detect a metallic precipitate formed in one or more discrete region(s).

With respect to Roth et al, Applicants note that M.P.E.P. 2141.02 cites *W.L. Gore & Associates Inc.* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from a claimed invention. Roth discloses a method for localizing and quantitating a molecule in a sample. In the method of Roth, an enzyme generates a colored reaction product which precipitates. However, as discussed above, the precipitate generated through enzymatic reactions is too diffuse to be used with an array having a density of at least 20 discrete regions per cm² as in the present invention.

Roth also discloses the use of antibodies having gold particles fixed thereto along with silver intensification in the context of localizing a molecule in a cell or tissue, a context which is significantly different than the microarrays utilized in the present invention. In addition, Roth teaches that methods using gold particles and silver intensification are undesirable or labor intensive in quantitative analyses (see Column 1, line 24-30). Accordingly, Roth teaches away from methods in which a metallic precipitate is used and therefore, as stated in M.P.E.P. 2141.02, does not teach or suggest the claimed invention.

Terstappen et al. disclose the use of magnetic beads to collect cells, specifically for separation of a target molecule. However, there is no disclosure or suggestion in Terstappen of detecting nucleic acids by the presence of a metallic precipitate in one or more discrete regions formed by a catalytic reduction on an array having a density of at least 20 discrete regions per cm² as in the present invention or devices comprising such arrays and such precipitates.

Because the combination of the cited references does not teach or suggest the claimed invention, Applicants respectfully submit that claims 1-26 are non-obvious in view of the above-combination of references.

Abouzied et al. in view of Van Ness et al. and Gingeras et al.

Claims 27, and 29-32 are rejected under 35 U.S.C. § 103(a) over Abouzied et al. in view of Van Ness et al. and Gingeras et al. Specifically, the Examiner asserts that it would have been obvious to one of skill in the art such that a CCD camera would have been linked to a computer with a program to recognize such images of discrete regions on the array in order to process the images taken by the camera, and to detect/quantitate the target compounds. The Examiner further asserts that the term "location" in [prior] claim 1 renders the claim indefinite, and that the apparatus taught/suggested by the references makes obvious the presently claimed invention.

Applicants submit that the term "location" is not present in amended claim 14 (of which the rejected claims are dependent upon). As discussed above, Claim 14 recites metallic precipitates formed by catalytic reduction of a metal. Neither of the cited references teach or

suggest the recited metallic precipitates formed by catalytic reduction of a metal. Therefore, the combination of cited references does not render the claimed invention obvious since they do not teach or suggest the invention as presently claimed.

Objective evidence of unexpected results relevant to issue of obviousness

According to M.P.E.P. 2141, objective evidence of unexpected results is relevant to the issue of obviousness. Applicants submit that the Declaration of Jose Remacle, dated November 19, 2001 provides objective evidence of unexpected results utilizing the method of the present invention. In particular, as provided in the Declaration dated Nov. 19, 2001, the metallic precipitates result in an improvement in sensitivity of over 1000 fold with respect to the methods disclosed in Van Ness (see Exhibit B, demonstrating that the limit of detection of spotted DNA for the metallic precipitate used in the present invention was 0.1 nM, while the peroxidase-based methods of Van Ness had a detection level of 100 nM). In addition, as provided in the Declaration, the metallic precipitates utilized in the present invention may be detected in a matter of minutes as opposed to the several hours required to detect the precipitates in the methods of Van Ness (see Exhibit C demonstrating that the metallic precipitate was obtained in 10 minutes as opposed to the peroxidase precipitate, which was formed after 3 hours). The high sensitivity and short reaction time are extremely beneficial in high throughput methods performed on high density arrays.

Furthermore, in the methods disclosed in Van Ness, the spots formed by the non-metallic precipitate resulting from the enzymatic reaction have a diameter of 50 micrometers. Such dimensions are not compatible with the high density arrays utilized in the present methods as they would not permit the differentiation of adjacent regions. In contrast, the metallic precipitates formed in the methods of the present invention may readily be localized to a single position on the high density arrays used in the methods of the present invention.

Applicants provide herewith an additional Declaration further demonstrating the advantages of the methods of the present invention. In particular, the accompanying Declaration demonstrates that the catalytic reduction of a metal to form a metallic precipitate provides a significant amplification of the signal relative to methods employing gold particles alone. In addition, the accompanying Declaration demonstrates that the present methods permit detection using infra-red light, thereby providing an enhanced signal/noise ratio relative to methods which employ visible light.

In view of the above remarks and accompanying Declaration, Applicants respectfully request withdrawal of the rejection to claims under 35 U.S.C. § 103(a).

Appl. No.
Filed

: 9/574,626
: May 19, 2000

V. Conclusion

Applicants submit amended claims 1, 2, 4, 5, 14 and 28 for consideration and entry. As stated above, the specification provides support for the amendments to the claims. Thus, no new matter has been added herewith. The changes made to the claims by the current amendment, including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment.

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Nov. 5, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended Four Times)** A method for the identification and/or the quantification of a target compound obtained from a sample, comprising the steps of:

putting into contact the target compound with a capture molecule in order to allow a specific binding between said target compound with a capture molecule, said capture molecule being fixed upon a surface of a solid support according to an array comprising a density of at least 20 discrete regions per cm², each of said discrete regions being fixed with one species of capture molecules;

performing a **[reaction]**catalytic reduction of a metal present in solution leading to formation of a metallic precipitate **[formed at the location of said binding by the deposit of a metallic compound]**in one or more discrete regions;

determining the possible presence of precipitate(s) in discrete region(s); and correlating the presence of the precipitate(s) at the discrete region(s) with the identification and/or a quantification of said target compound.

2. **(Twice Amended)** The method according to Claim 1, wherein the **[reaction]**catalytic reduction leading to the formation of **[a]**the metallic precipitate is obtained by the precipitation of a metallic compound upon the bound target compound.

4. **(Twice Amended)** The method according to Claim 1, wherein the **[reaction]**catalytic reduction leading to the formation of the metallic precipitate is a reduction of a metal in the presence of an enzyme.

5. **(Twice Amended)** The method according to Claim 1, wherein the **[reaction]**catalytic reduction leading to the formation of the metallic precipitate is a chemical reduction of silver in the presence of colloidal gold particles coupled to the bound target compound.

14. **(Amended Four Times)** A diagnostic and/or quantification apparatus comprising:

a solid support comprising an array comprising at least 20 discrete regions per cm², each of said regions being fixed with one species of a capture molecule which recognizes a target compound, said target compounds bound to some of said capture

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molecule[s] leading to a catalytic reduction of a metal present in solution, and a formation of a metallic precipitate in one or more discrete region(s) **[precipitate present at the location of said bound target compounds];**

a detection and/or quantification device for detecting said precipitate in said discrete region(s); and

a computer programmed to collect the results obtained from said detection and/or quantification device.

28. **(Amended)** The method of Claim 1, wherein said metallic precipitate is formed on the surface of a particle associated with said target compound.